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(54) **5-Pyridyl-1,3-thiazole derivatives, their production and use.**

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**GB-A- 1 112 128**
**US-A- 3 557 135**
**US-A- 3 578 671**
**US-A- 3 705 153**
**US-A- 3 963 735**

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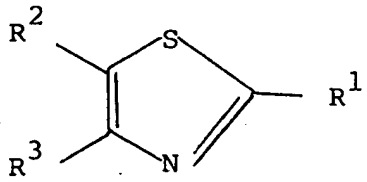
## Descripti n

This invention relates to novel 5-pyridyl-1,3-thiazole derivatives having, among others, analgesic, anti-pyretic, anti-inflammatory, anti-ulcer, thromboxane $A_2(TXA_2)$ synthetase inhibiting, or platelet aggregation inhibiting actions, to a method of preparing same and to pharmaceutical compositions containing same.

DE-A-1 062 245, US-A-3 705 153 and US-A-3 963 735 disclose a variety of 2,4,5-substituted 1,3-thiazole derivatives. US-A-3 578 671 and US-A-3 557 135 disclose 2,4,5-substituted oxazole derivatives.

Substantially no derivatives of 5-pyridyl-1,3-thiazole have been known. The present inventors synthesized a variety of novel 5-pyridyl-1,3-thiazole derivatives, and subjected them to biological tests to find that those compounds had pharmacological actions such as analgesic, anti-pyretic, anti-inflammatory, anti-ulcer, thromboxane $A_2(TXA_2)$ synthetase inhibitory or platelet aggregation inhibiting actions.

This invention provides a compound of the formula:



(I)

wherein

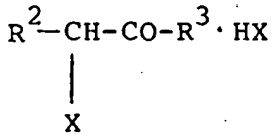
$R_1$ is (1) a $C_{1-10}$ alkyl group unsubstituted or substituted by $C_{1-4}$ alkylamino or carboxyl, (2) a phenyl group unsubstituted or substituted by carboxyl, (3) a $C_{3-7}$ cycloalkyl group, (4) an amino group unsubstituted or substituted by $C_{1-4}$ alkyl, phenyl or pyridyl, (5) a piperidino group or (6) a morpholino group,

$R_2$ is a pyridyl group unsubstituted or substituted by $C_{1-4}$ alkyl, and

$R_3$ is a naphthyl or a phenyl group unsubstituted or substituted by $C_{1-4}$ alkoxy, hydroxy, halogen, methylenedioxy or trimethylene,

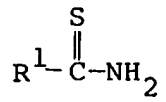
or a salt thereof.

The invention also provides a method of preparing a 1,3-thiazole derivative as defined above, or a salt thereof, characterised by allowing a compound representable by the general formula;



(II)

[wherein $R^2$ and $R^3$ have the meanings as defined above, and X stands for a halogen atom] to react with a compound representable by the general formula;



(III)

[wherein $R^1$ has the meaning as defined above.

The invention further provides an analgesic, anti-pyretic, anti-inflammatory and anti-ulcer pharmaceutical composition, which comprises, as an active ingredient, an effective amount of a compound as defined above, or a salt thereof, and a pharmaceutically acceptable carrier therefor.

In the above-mentioned general formulas (I) and (III), alkyl groups represented by $R^1$ are those having 1-10 carbon atoms such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, n-hexyl, n-ocyl, n-nonyl or n-decyl; cycloalkyl groups represented by $R^1$ are those having 3-7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; and heterocyclic groups having carbon as the bonding

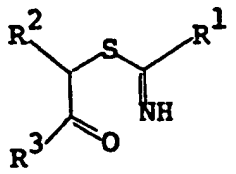
hand representable by $R^1$ are ones containing in its ring one or optional substituents of the alkyl groups are alkylamino having 1-4 carbon atoms, e.g. methylamino, ethylamino or propylamino, and carboxyl. The optional carboxyl substituents of the phenyl group can take any position of the cyclic structure. The amino group represented by $R^1$ may also be substituted by a lower alkyl having 1-4 carbon atoms, e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl, or by phenyl or pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-methyl-3-pyridyl, 4-methyl-2-pyridyl, or 2-methyl-3-pyridyl), and the number of these substituents may be one or two.

In the general formulae (I) and (II), as the pyridyl group representable by $R^2$, any one of 2-pyridyl, 3-pyridyl or 4-pyridyl may be employed though among them 3-pyridyl is the most preferable, and these may have as a substituent at an optional position of the ring an alkyl group having one to four carbon atoms, i.e. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl.

In the general formulae (I) and (II) phenyl group representable by $R^3$ may have as the substituent at optional positions of the ring one to three of $C_{1-4}$ alkoxy (e.g. methoxy, ethoxy and n-propoxy), hydroxyl or halogen. As the halogen there may be mentioned fluorine, chlorine, bromine and iodine. The group representable by $R^3$ may have at its optional adjacent position on the ring methylenedioxy or trimethylene group as the substituent.

Compounds representable by the general formula (I) may be addition salts of a pharmacologically acceptable organic acid or inorganic acid. As the acid addition salts there may be mentioned for example ones with hydrochloric acid, hydrobromic acid, phosphoric acid, oxalic acid and methanesulfonic acid.

A compound representable by the general formula (I) can be produced by allowing a compound representable by the general formula (II) with a compound representable by the general formula (III) in the presence of a basic substance. This reaction is usually conducted in a solvent e.g. water, alcohol, acetonitrile, tetrahydrofuran, dimethyl-formamide and 1,2-dimethoxyethane. The molar ratio of a compound (II) to a compound (III) to be brought into contact with each other is preferably 1 : 1-1.2. As the basic substance, there may be mentioned for example triethylamine, sodium hydroxide, sodium carbonate and potassium carbonate. The molar ratio of a basic substance to be used is usually within the range from 2.0 to 3.0 relative to the compound (II), preferably 2.0-2.5. The reaction temperature is usually within the range from 0 °C to the boiling point of the solvent used. In this reaction, as the first stage, a compound (II) reacts with a compound (III) to afford a compound representable by the general formula (IV);




(IV)

[wherein $R^1$, $R^2$ and $R^3$ are of the same meaning as defined above], which undergoes to ring-closure reaction to give a compound (I). In order to conduct these reactions more advantageously, it is preferable to bring a compound (II) into contact with a compound (III) at a temperature not higher than room temperature, then the reaction mixture is heated to a temperature higher than room temperature.

Thus-obtained compound (I) can be isolated and purified by a conventional isolation and purification means such as chromatography, solvent-extraction, crystallization and recrystallization.

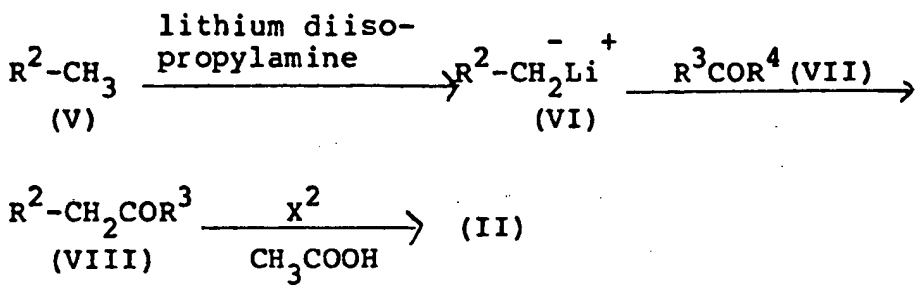
The compounds (I) and their salts show excellent anti-pyretic action, analgesic action, anti-inflammatory action, anti-ulcer action, platelet aggregation controlling action and thromboxane $A_2$ synthesis inhibiting action, and the toxicity thereof is very weak. Thus the compounds (I) can be administered with high safety.

Therefore, the compounds of this invention can be administered to mammals (e.g. human, monkey, cat, dog, horse, cow, mouse, rat etc.) for the therapy of pain, inflammatory diseases, rheumatic chronic diseases, gastroenteric ulcers, ischemic circulation disturbance due to platelet aggregation. They can be orally administered in the form of e.g. tablets, capsules, powder and granule, or non-orally administered in the form of e.g. injection or pellet. The pharmaceutical composition can be prepared by mixing the compound (I) or salt thereof with pharmaceutical acceptable carriers by a conventional manner. The dosage is usually 1 to 10 mg/kg (e.g. 50-500 mg/day/adult) orally and 1 to 20 mg/kg (e.g. 50-200 mg/day/adult) non-orally, and 1-3 times daily.

Among the compounds representable by the general formula (I), 4-[4-phenyl-5-(3-pyridyl)-1,3-thiazole]-butyric acid and 4-[4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole]butyric acid have particularly excellent thromboxane synthetase inhibiting action, and 2-phenyl-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole, 2-cyclohexyl-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole and 2-cyclohexyl-4-phenyl-5-(3-pyridyl)-1,3-

thiazole have partienlarly excellent platelet aggregation controlling action, and 2-amino-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole, 2-methylamino-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole, 2-ethyl-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole, 2-methylamino-4-(3,4-methylenedioxyphenyl)-5-(3-pyridyl)-1,3-thiazole, 2-methylamino-4-(3,4-trimethylenephenylene)-5-(3-pyridyl)-1,3-thiazole, 2-ethylamino-4-(3,4-methylenedioxyphenyl)-5-(3-pyridyl)-1,3-thiazole, and 2-ethylamino-4-(5-indanyl)-5-(3-pyridyl)-1,3-thiazole have particularly excellent analgesic, antipyretic and anti-ulcer actions.

Compounds representable by the general formula (II) can be prepared by, for example, the following process;



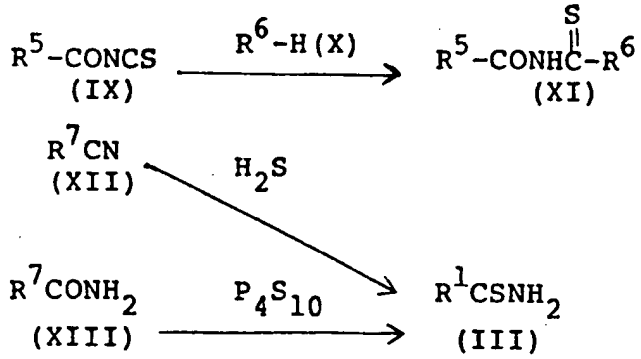

[wherein $R^2$, $R^3$ and X are of the same meaning as defined above, and $R^4$ stands for a lower alkoxy group having 1-4 carbon atoms, e.g. methoxy and ethoxy, or dimethylamino, diethylamino, N-phenyl-N-methylamino, N-methoxy-methylamino, pyrrolidino, morphorino and methyl aziridino]

The reaction for leading a compound (V) to a compound (VI) is conducted by allowing the former to react with lithium diisopropylamine. This reaction is usually carried out in a solvent, e.g. anhydrous tetrahydrofuran or anhydrous diethylether at a temperature ranging from -70 °C to 10 °C.

The reaction for leading a compound (VI) to a compound (VIII) is conducted by allowing the former to react with a compound (VII). This reaction is usually carried out in a solvent, e.g. as in the above, anhydrous tetrahydrofuran or anhydrous diethylether at a temperature ranging from 0 °C to 20 °C.

By allowing a halogen to react with a compound (VIII), a compound (II) can be obtained. This reaction is conducted by allowing a halogen e.g. chlorine or bromine to react with a compound (VIII) in a solvent such as acetic acid. The reaction temperature usually ranges from 10 °C to 100 °C and the reaction time usually ranges from one to ten hours. The reaction product is allowed to precipitate as insoluble salt by addition of ether, isopropylether or the like, then the solvent is removed, followed by crystallization of the residue from ethanol, ethyl acetate, methanol or the like for refining.

Compounds representable by the general formula (III) can be prepared by, for example, the following process;




[wherein $R^1$ is of the same meaning as defined above, $R^5$ stands for methoxy, ethoxy or phenyl group, $R^6$ stands for a cyclic amino, di-substituted lower alkylamino or diphenylamino group, and $R^7$ stands for substituent shown by $R^1$ except di-substituted amino].

For leading a compound (IX) to a compound (XI), the former is allowed to react with a compound (X). This reaction is conducted in an organic solvent. As the solvent are mentioned, for example, methylene chloride and chloroform. The ratio of a compound (IX) to be brought into contact with a compound (X) is

usually 1.0-1.5 mol. relative to 1 mol. of a compound (IX). The reaction temperature usually ranges from 0 °C to 50 °C, and the reaction time is usually within the range from one to five hours.

For leading a compound (XI) to a compound (III), a conventional alkaline or acid hydrolysis is usually employed. For the alkaline hydrolysis is used sodium hydroxide or potassium hydroxide, and for the acid hydrolysis is used hydrochloric acid or bromic acid. As a solvent is employed water or an aqueous organic solvent (ethanol, methanol, dioxane, etc.).

For leading a compound (XII) to a compound (XIV), the former compound is allowed to react with hydrogen sulfide under basic conditions. As a base is preferably employed triethylamine or pyridine, and as a reaction solvent is employed, for example, methylene chloride, chloroform, triethylamine or pyridine. The reaction is usually conducted at a temperature ranging from -10 °C to 30 °C under normal pressure or elevated pressure.

For leading a compound (XIII) to a compound (III), the former compound is allowed to react with $P_4S_{10}$. This reaction is conducted in an organic solvent such as ether, tetrahydrofuran, methylene chloride and chloroform at a temperature ranging from room temperature to the boiling point of a solvent employed. The amount of phosphorus pentasulfide (as $P_4S_{10}$) is within the range of from 0.5 mol to 1.2 mol relative to the compound (XIII).

The following working examples, experimental examples and reference examples will explain the present invention more concretely.

Example 1

In 18 mℓ of acetonitrile was dissolved 242 mg of N-methylthiourea. In the solution was suspended 1.0 g of 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide. To the suspension was added dropwise slowly 0.4 mℓ of triethylamine while stirring. The mixture was stirred for three hours at refluxing temperature, and the solvent was evaporated off. To the residue was added a saturated aqueous solution of sodium hydrogen carbonate. The mixture was subjected to extraction with ethyl acetate. The extract was dried, then the solvent was evaporated off. The residue was recrystallized from ethyl acetate - isopropyl ether to yield 650 mg (85%) of 4-(4-methoxyphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazole, m.p. 158-159 °C.

Example 2

In 40 mℓ of acetonitrile was dissolved 516 mg of thiourea. In the solution was suspended 2.5 g of 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)-ethanone hydrobromide. To the suspension was added dropwise slowly 0.95 mℓ of triethylamine while stirring. The mixture was stirred for 3 hours at a refluxing temperature which was then left standing for cooling. Precipitating crystals were collected by filtration. The crystals were washed with an aqueous solution of saturated hydrogen carbonate, water, ethanol add ethylether in that order, followed by drying. The crystals were recrystallised from tetrahydrofuran to yield 1.5 g (90%) of 2-amino-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazol, m.p. 265-266 °C.

Example 3

In 40 mℓ of acetonitrile was dissolved 493 mg of thiopropionic acid amide. In the solution was suspended 2.15 g of 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone To the suspension was added dropwise slowly 0.78 mℓ of triethylamine while stirring. The mixture was stirred for 3 hours at a refluxing temperature, then the solvent was evaporated off. To the residue was added a saturated aqueous solution of sodium hydrogen carbonate. The mixture was subjected to extraction with ethyl acetate. The extract was dried, then the solvent was evaporated off. The residue was recrystallised from ethyl acetate-isopropyl ether to yield 1.38 g (91%) of 2-ethyl-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole, m.p. 59-60 °C.

Example 4

In 40 mℓ of acetonitrile was suspended 2.26 g of 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide. To the suspension was added 1.0 g of 4-methoxycarbonyl butane thioamid . To the mixture was added dropwise 0.8 mℓ of triethylamine while stirring. The mixture was stirred for 3 hours at a refluxing temperature. The solvent was evaporated off. To the residue was added a saturated aqueous solution of sodium hydrogen carbonate. The resultant was subjected to extraction with ethyl acetate, and the extract was washed with water, dried and concentrated. The concentrate was purified by means of a silica-gel

column chromatography [ethyl acetate-isopropylether (1:1)] to yield 1.5 g (72.6%) of 2-(3-methoxycarbonylpropyl)-4-(4-methoxyphenyl)-5-pyridyl)-1,3-thiazole as an oily substance.

Example 5

In 5 mℓ of methanol was dissolved 1.5 g of 2-(3-methoxycarbonylpropyl)-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole obtained in Example 4. To the solution was added 1.5 g of sodium hydroxide dissolved in 5 mℓ of water. The mixture was stirred for 2 hours at 80° C. To the resultant was added water, pH of which was adjusted to 6.0 with 1N-HCℓ. The aqueous solution was subjected to extraction with ethyl acetate. The organic layer was washed with water, dried and concentrated. The resulting crystals were recrystallised from ethyl acetate to yield 1.2 g (83%) of 2-(3-carboxypropyl)-4-(4-methoyphenyl)-5-(3-pyridyl)-1,3-thiazole, m.p. 163-164° C.

Example 6

In 10 mℓ of tetrahydrofuran was dissolved 770 mg of 2-(3-methoxycarbonylpropyl)-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole prepared by example 4, which was then cooled with ice. To the solution was added little by little 100 mg of lithium aluminium hydride, which was stirred for one hour. To the mixture was added water, which was subjected to extraction with ethyl acetate. The organic layer was washed with water, dried and concentrated, followed by purifying by means of a silica-gel chromatography [chloroform-methanol (9:1)] to yield 576 mg (81%) of 2-(4-hydroxybutyl)-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole as an oily substance.

Example 7

In 5 mℓ of dimethylformamide was dissolved 1 g of 2-amino-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole. To the solution was added under ice-cooling 580 mg of ethoxycarbonylacetylchloride.The mixture was stirred for 30 minutes, to which was then added a saturated aqueous solution of sodium hydrogen chloride. The resultant was subjected to extraction with ethyl acetate. The organic layer was washed with water, dried and concentrated, followed by recrystallization from tetrahydrofuran to give 850 mg (61%) of 2-ethoxycarbonylacetylamino-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole, m.p. 202-203° C.

Example 8

To 15 mℓ of acetonitrile were added 1.0 g of 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide and 387 mg 1-piperazine carbothioamide. To the mixture was slowly added 0.4 mℓ of triethylamine while stirring. The whole mixture was stirred for 2 hours at refluxing temperature, then the solvent was evaporated off. To the residue was added a saturated aqueous solution of sodium hydrogen carbonate, which was subjected to extraction with ethyl acetate. The extract was dried and the solvent was evaporated off. The residue was dissolved in 2 mℓ of pyridine, and the solution was cooled with ice, to which was added 0.3 mℓ of acetylchloride. The mixture was left standing at room temperature for one hour. The reaction solution was poured into ice-water, followed by extraction with ethyl acetate. The extract solution was washed with water, dried and concentrated. The concentrate was purified by means of a silica-gel column chromatography [ethyl acetate - methanol (9:1)] to yield 300 mg (28%) of 2-(4-acetyl-1-piperazinyl)-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole.

Example 9

In 3.2 mℓ of 1% MeOH-HCℓ was dissolved 2-amino-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole The solvent was evaporated off. The residue was recrystallized from methanol-ethyl acetate to yield 180 mg (80%) of 2-amino-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole hydrochloride, m.p. 145-150° C.

Example 10

In 40 mℓ of acetonitrile was dissolved 661 mg. of N-methyl thiourea. In the solution was suspended 2.9 g of 2-bromo-1-(5-indanyl)-2-(3-pyridyl)ethanone hydrobromide. To the suspension was added dropwise slowly 1 mℓ of triethylamine. The mixture was then stirred for 2 hours at refluxing temperature, followed by being left standing for cooling. The solvent was then evaporated off. To the residue was added a saturated

aqueous solution of sodium hydrogen carbonate. The mixture was subjected to extraction with ethyl acetate. The extract solution was washed with water, dried and, then, the solvent was evaporated off. Recrystallization was conducted from ethyl acetate-isopropylether afforded 1.8 g (80%) of 4-(5-indanyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazole, m.p. 169-170 °C.

Example 11

In 40 mℓ of acetonitrile was dissolved 1.12 g of benzyloxycarbonylaminothioacetamide. In the solution was suspended 2.0 g of 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide. To the suspension was added while stirring 0.8 mℓ of triethylamine. The mixture was stirred for 2 hours under reflux. The resultant was left standing for cooling, then the solvent was evaporated off. To the residue was added a saturated aqueous solution of sodium hydrogen carbonate. The mixture was subjected to extraction with ethyl acetate. The extract solution was washed with water, dried and, then, the solvent was evaporated off. The residue was recrystallized from ethyl acetate-isopropylether to give 1.3 g (yield 56%) of 2-(benzyloxycarbonylaminomethyl)-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole, m.p. 93-94 °C.

Example 12

In 10 mℓ of tetrahydrofuran was dissolved 1.2 g of 2-(benzyloxycarbonylaminomethyl)-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole obtained by Example 11. To the solution was added 10 mℓ of 5N-HCℓ, and the mixture was stirred for 2 hours at 80 °C. Tetrahydrofuran was evaporated off under reduced pressure. The remaining aqueous layer was made alkaline with 2N-NaOH, which was subjected to extraction with ethyl acetate. The extract was washed with water and dried, then the solvent was evaporated off. The residue was purified by means of a silica-gel column chromatography [eluent: chloroform-methanol (9:1)] to give 0.5 g (yield 60%) of 2-(aminomethyl)-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole.

Example 13

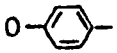
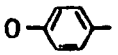
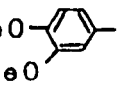
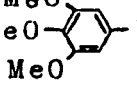
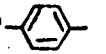
In 50 mℓ of acetonitrile was dissolved 2.3 g of N-methylbenzoylaminothioacetamide. In the solution was suspended 4.0 g of 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide To the suspension was added while stirring 1.5 mℓ of triethylamine, followed by further stirring under reflux. The reaction solution was left standing for cooling, then the solvent was evaporated off. To the residue was added a saturated aqueous solution of sodium hydrogen carbonate. The mixture was subjected to extraction with ethyl acetate. The extract solution was washed with water, dried, then, the solvent was evaporated off. The residue was purified by means of a silica-gel column chromatography (eluent: ethyl acetate) to give 3.2 g (yield 72%) of 2-(N-methylbenzoylaminomethyl)-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole.

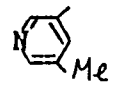
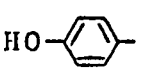
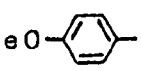
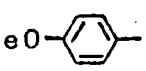
Example 14

To 2-(N-methyl(benzoylaminomethyl)-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole obtained by Example 13 was added 20 mℓ of 5N-HCℓ, and the mixture was stirred for 2 hours at 80 °C. The reaction solution was left standing for cooling, which was then made alkaline with 2N-NaOH. The alkaline solution was subjected to extraction with ethyl acetate. The extract solution was washed with water, dried and concentrated under reduced pressure, followed by purification by means of a silica-gel column chromatography [eluent: chloroform-methanol (9:1)] to give 2.1 g (yield 91%) of 4-(4-methoxyphenyl)-2-methylaminomethyl-5-(3-pyridyl)-1,3-thiazole.

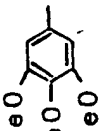
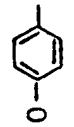
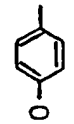
Compounds prepared after the manner described in the above Examples 1-9 are exemplified in Table 1. Melting points are all uncorrected.

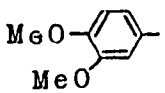
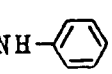
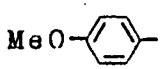
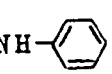
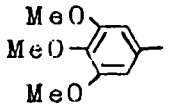
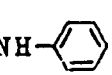
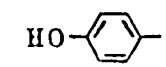
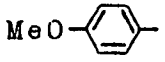
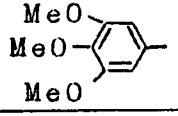
Table 1

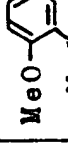
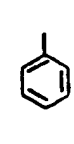
| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 1 | 1 | -NHMe |  |  | $C_{16}H_{15}N_3OS$ 158-159° |
| 2 | 2 | $-NH_2$ |  |  | $C_{15}H_{13}N_3OS$ 265-266° |
| 3 | 1 | -NHMe |  |  | $C_{15}H_{13}N_3S$ 168-169° |
| 4 | 2 | $-NH_2$ |  |  | $C_{14}H_{11}N_3S$ 253-254° |
| 5 | 2 | $-NH_2$ |  |  | $C_{16}H_{15}N_3O_2S$ 240-241° |
| 6 | 2 | $-NH_2$ |  |  | $C_{17}H_{17}N_3O_3S$ 168-169° |
| 7 | 1 | -NHMe |  |  | $C_{15}H_{12}N_3FS$ 157-158° |

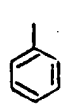
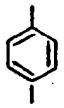
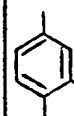
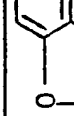
| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 8 | 1 | -NHMe |  |  | $C_{16}H_{15}N_3S$ 205-206° |
| 9 | 2 | $-NH_2$ |  |  | $C_{14}H_{11}N_3OS$ 266-268° |
| 10 | 7 | -NHCOMe |  |  | $C_{17}H_{15}N_3O_2S$ 119-120° |
| 11 | 7 | $-NHCOCH_2CO_2Et$ |  |  | $C_{20}H_{19}N_3O_4S$ 201-202° |
| 12 | 7 | $-NHCOCH_2CO_2Me$ |  |  | $C_{18}H_{15}N_3O_3S$ 185-186° |
| 13 | 2 | $-NH_2$ |  |  | $C_{14}H_{11}N_3S$ 236-237° |
| 14 | 1 | -NHMe |  |  | $C_{15}H_{13}N_3S$ 215-216° |

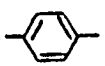
| Cmpd No. | No. of w. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 15 | 1 | $-NHMe$ |  |  | $C_{16}H_{15}N_3OS$ 214–215° |
| 16 | 2 | $-NH_2$ |  |  | $C_{15}H_{13}N_3OS$ 217–218° |
| 17 | 2 | $-NH_2$ |  |  | $C_{15}H_{13}N_3OS$ 282–284° |
| 18 | 2 | $-NH_2$ |  |  | $C_{14}H_{11}N_3S$ 248–250° |
| 19 | 1 | $-NHMe$ |  |  | $C_{16}H_{15}N_3OS$ 177–178° |
| 20 | 1 |  |  |  | $C_{20}H_{21}N_3OS$ 130–131° |
| 21 | 1 |  |  |  | $C_{19}H_{19}N_3O_2S$ 134–135° |

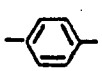
| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 22 | 3 | $-CH_2CH_3$ |  |  | $C_{19}H_{20}N_2O_3S$ 84-84.5° |
| 23 | 3 | $-CH_2CH_3$ |  |  | $C_{17}H_{16}N_2OS$ 59-60° |
| 24 | 3 | $-CH_2CH_3$ |  |  | $C_{16}H_{14}N_2OS$ 174-175° |
| 25 | 3 | $-CH_3$ |  |  | $C_{16}H_{14}N_2OS$ 113-114° |
| 26 | 3 | $-CH_2CH_3$ |  |  | $C_{16}H_{14}N_2S$ |
| 27 | 3 |  |  |  | $C_{20}H_{14}N_2S$ 135-136° |
| 28 | 3 |  |  |  | $C_{21}H_{16}N_2OS$ 104-105° |

| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 29 | 3 |  |  |  | $C_{22}H_{18}N_2O_2S$ 96- 98° |
| 30 | 1 |  |  |  | $C_{21}H_{17}N_3OS$ 195-196° |
| 31 | 1 |  |  |  | $C_{23}H_{21}N_3O_3S$ 211-213° |
| 32 | 1 |  |  |  | $C_{20}H_{15}N_3OS$ 280-282° |
| 33 | 3 |  |  |  | $C_{20}H_{20}N_2S$ 100-101° |
| 34 | 3 |  |  |  | $C_{21}H_{22}N_2OS$ 92- 93° |
| 35 | 3 |  |  |  | $C_{23}H_{26}N_2O_3S$ 111-112° |

| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Compositin Formula m.p. |
|---|---|---|---|---|---|
| 36 | 4,5 |  |  |  | $C_{22}H_{18}N_2O_3$ S 264-265° |
| 37 | 4,5 |  |  |  | $C_{23}H_{18}N_2O_4$ S 245-246° |
| 38 | 4,5 |  |  |  | $C_{24}H_{20}O_6N_2$ S 247-248° |
| 39 | 3 | -Me |  |  | $C_{18}H_{14}N_2O_2$ S 208-209° |
| 40 | 4,5 |  |  |  | $C_{23}H_{16}O_2N_2$ S 255-256° |
| 41 | 4,5 |  |  |  | $C_{26}H_{22}O_4N_2$ S 225-226° |
| 42 | 4,5 | $-(CH_2)_3COOH$ |  |  | $C_{18}H_{16}N_2O_2$ S 143-144° |

| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 43 | 4,5 | $-(CH_2)_3COOH$ |  |  | $C_{19}H_{18}N_2O_3S$ 163-164° |
| 44 | 4,5 | $-(CH_2)_3COOH$ |  |  | $C_{19}H_{18}N_2O_2S$ 134-135° |
| 45 | 4,5 | $-(CH_2)_8COOH$ |  |  | $C_{23}H_{26}N_2O_2S$ 112-113° |
| 46 | 4,6 | $-(CH_2)_4OH$ |  |  | $C_{18}H_{18}N_2OS$ 51- 52° |
| 47 | 1 | $-NHCH_2CH_3$ |  |  | $C_{17}H_{17}N_3OS$ 154-155° |
| 48 | 1 | $-NHMe$ |  |  | $C_{18}H_{13}N_3O_2S$ 187-188° |
| 49 | 1 | $-NHMe$ |  |  | $C_{17}H_{17}N_3S$ 124-125° |

| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 50 | 9 | $-NH_2$ |  | MeO-  | $C_{15}H_{13}N_3OS \cdot HCl$ 145-150° |
| 51 | 1 | -NHMe |  |  | $C_{15}H_{13}N_3S$ 191-192° |

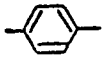
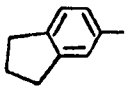
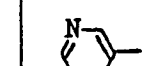
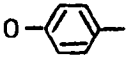
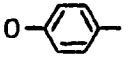
| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula | NMR δ ppm($CDCl_3$) |
|---|---|---|---|---|---|---|
| 52 | 1 | $-N(C_2H_5)_2$ |  | MeO-  | $C_{19}H_{21}N_3OS$ | 1.27(6H),3.52(4H),3.77(3H),6.78(2H),7.07(1H),7.40(2H),7.50(1H),8.37(1H),8.50(1H) |
| 53 | 8 | -N  NCOMe |  | MeO-  | $C_{21}H_{22}N_4O_2S$ | 2.13(3H)3.60(6H),3.77(5H),6.78(2H),7.17(1H),7.38(2H),7.53(1H),8.42(1H),8.52(1H) |

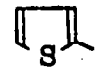
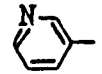
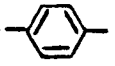
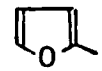
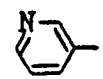
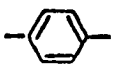
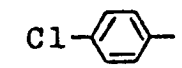
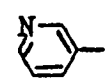
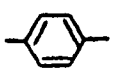
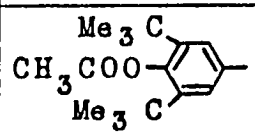
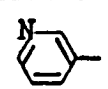
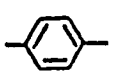
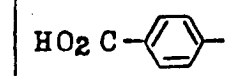
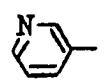
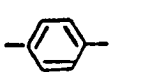
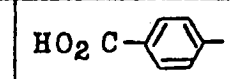
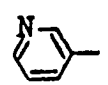
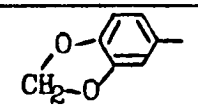
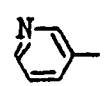
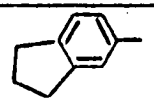
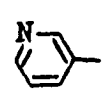
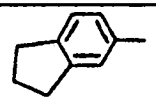
| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula | NMR $\delta$ ppm ($CDCl_3$) |
|---|---|---|---|---|---|---|
| 54 | 1 | $-N(Me)_2$ |  |  | $C_{17}H_{17}N_3OS$ | 3.12(6H),3.77(3H),6.78 (2H),7.07(1H)7.40 (2H), 7.50(1H),8.37(1H),8.50 (1H) |
| 55 | 3 | $-CH_2CH_3$ |  |  | $C_{18}H_{18}N_2O_2S$ | 1.43(3H),3.07(2H),3.70 (3H),3.87(3H),6.75(1H), 7.00(2H),7.20(1H),7.60 (1H),8.48(1H),8.60(1H) |
| 56 | 3 | $-CH_2CH_3$ |  |  | $C_{16}H_{14}N_2S$ | 1.40(3H),3.05(2H),6.87 (1H),7.27(5H),7.57(1H), 8.47(1H),8.57(1H) |
| 57 | 3 | $-CH_2CH_2CH_2CH_3$ |  |  | $C_{18}H_{18}N_2S$ | 0.97(3H),1.48(2H),1.85 (2H),3.05(2H),7.23(1H), 7.27(5H),7.57(1H),8.50 (1H),8.57(1H) |
| 58 | 3 | $-CH_2CH_3$ |  |  | $C_{17}H_{16}N_2OS$ | 1.43(3H),3.07(2H),3.80 (3H),6.83(2H),7.18(2H), 7.43(2H),8.50(2H) |

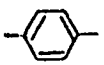
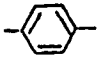
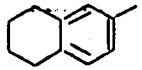
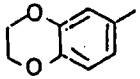
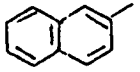
| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula | NMR $\delta$ ppm($CDCl_3$) |
|---|---|---|---|---|---|---|
| 59 | 3 |  |  |  | $C_{22}H_{24}N_2O_2S$ | 3.73(3H)\3.87 (3H),6.80 (1H),7.00~7.80(7H), 8.03(2H),8.53(1H),8.67 (1H) |
| 60 | 4,5 | $-CH_2COOH$ |  |  | $C_{16}H_{12}N_2O_2S$ | 2.77(2H),7.20-7.70 (7H),8.60(2H),10.40 (1H) |
| 61 | 4 | $-(CH_2)_3COOMe$ |  |  | $C_{19}H_{18}N_2O_2S$ | 2.00(2H),2.17(2H),2.50 (2H),3.59(3H),3.67(3H), 7.17(1H),7.30(5H),7.82 (1H),8.47(1H),8.70(1H) |
| 62 | 4,5 | $-(CH_2)_6COOH$ |  |  | $C_{20}H_{20}N_2O_2S$ | 1.40-2.10(6H),2.37 (2H),3.05(2H),7.10-7.70 (7H),8.50(1H),8.57(1H), 10.50(1H) |
| 63 | 4,5 | $-(CH_2)_6COOH$ |  |  | $C_{22}H_{24}N_2O_4S$ | 1.40-2.10(6H),2.37(2H), 3.07(2H),3.70(3H),3.83 (3H),6.75(1H),6.97(2H), 7.23(1H),7.63(1H),8.50 (1H),8.60(1H),10.10(1H) |

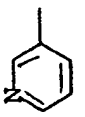
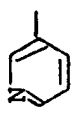
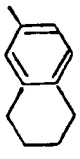
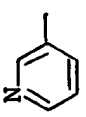
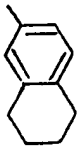
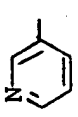
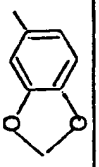
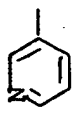
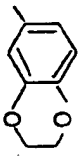
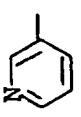
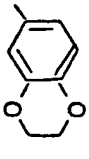
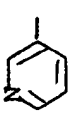
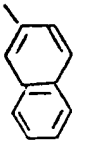
| Cmpd No. | No.of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula | NMR δ ppm(CDCl3) |
|---|---|---|---|---|---|---|
| 64 | 4,6 | $-(CH_2)_4OH$ |  |  | $C_{19}H_{20}N_2O_2S$ | 1.60-2.20(5H),3.07(2H), 3.70(2H),3.77(3H),6.80 (2H),7.20(1H),7.37(2H), 7.58(1H),8.50(1H),8.57(1H) |
| 65 | 4,6 | $-(CH_2)_6OH$ |  |  | $C_{21}H_{24}N_2O_2S$ | 1.40-2.00(8H),2.30(1H), 3.03(2H),3.60(2H),3.77 (3H),6.80(2H),7.26(1H), 7.40(2H),7.60(1H),8.47 (1H),8.56(1H) |
| 66 | 3 | $-CH_2CH_2CH_3$ |  |  | $C_{18}H_{18}N_2OS$ | 1.03(3H),1.87(2H),3.00 (2H),3.77(3H),6.78(2H), 7.17(1H),7.38(2H),7.57 (1H),8.47(1H),8.57(1H) |
| 67 | 3 |  |  |  | $C_{18}H_{18}N_2OS$ | 1.40(3H),1.50(3H),3.35 (1H),3.77(3H),6.78(2H), 7.17(1H),7.38(2H),7.58 (1H),8.47(1H),8.57(1H) |

| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 68 | 1 | $N(Me)_2$ |  |  | $C_{17}H_{16}N_3O_2S$ 76–77° |
| 69 | 1 | $N(CH_2CH_3)_2$ |  |  | $C_{19}H_{19}N_3O_2S$ 97–98° |
| 70 | 1 | NHMe |  |  | $C_{16}H_{13}N_3O_2S$ 234–235° |
| 71 | 1 | $N(Me)_2$ |  |  | $C_{17}H_{15}N_3O_2S$ 144–145° |
| 72 | 1 | NHMe |  |  | $C_{16}H_{15}N_3OS$ 146–147° |
| 73 | 1 | NHMe |  |  | $C_{16}H_{15}N_3OS$ 153–154° |
| 74 | 1 | NHMe |  |  | $C_{15}H_{12}N_3FS$ 205–206° |

| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 75 | 1 | NHMe |  |  | $C_{15}H_{12}N_3Cl$S 224-225° |
| 76 | 1 | NHMe |  |  | $C_{15}H_{12}N_3Br$S 206-207° |
| 77 | 1 | NHMe |  |  | $C_{15}H_{13}N_3$S 191-192° |
| 78 | 1 | NHMe |  |  | $C_{15}H_{13}N_3$S 144-145° |
| 79 | 10 | NHMe |  |  | $C_{18}H_{17}N_3$S 169-170° |
| 80 | 1 |  |  |  | $C_{23}H_{21}N_3O$S 126-127° |
| 81 | 1 |  |  |  | $C_{20}H_{16}N_4O$S 222-223° |

| Cmpd No. | No.of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 82 | 3 |  |  |  | $C_{19}H_{14}N_2OS_2$ 132-133° |
| 83 | 3 |  |  |  | $C_{19}H_{14}N_2O_2S$ 90- 91° |
| 84 | 3 |  |  |  | $C_{21}H_{15}N_2OClS$ 148-149° |
| 85 | 3 |  |  |  | $C_{31}H_{34}N_2O_3S$ 180-181° |
| 86 | 4,5 |  |  |  | $C_{21}H_{13}N_2O_2SF$ 240-241° |
| 87 | 4,5 |  |  |  | $C_{22}H_{14}N_2O_4S$ 258-259° |
| 88 | 10 | $N(Me)_2$ |  |  | $C_{19}H_{19}N_3S$ 85- 86° |
| 89 | 10 | $N(CH_2CH_3)_2$ |  |  | $C_{21}H_{23}N_3S$ 56- 57° |

| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula | NMR δ ppm (CDCl3) |
|---|---|---|---|---|---|---|
| 90 | 11,12 | $CH_2NH_2$ |  |  | $C_{16}H_{15}N_3OS$ | 1.90(2H),3.80(3H),4.20 (2H),6.80(2H),7.27(1H), 7.38(2H),7.62(1H),8.50 (1H),8.60(1H) |
| 91 | 13,14 | $CH_2NHMe$ |  |  | $C_{17}H_{17}N_3OS$ | 1.86(1H),2.60(3H),3.78 (3H),4.10(2H),6.82(2H), 7.27(1H),7.37(2H),7.62 (1H),8.50(1H),8.60(1H) |
| 92 | 1 | $-NMe_2$ |  |  | $C_{20}H_{21}N_3S$ oil | 1.73(4H),2.68(4H), 3.10(6H), 6.90(1H), 7.00-7.30(3H),7.53(1H) 8.37(1H),8.50(1H) |
| 93 | 1 | $-NMe_2$ |  |  | $C_{18}H_{17}N_3O_2S$ oil | 3.13(6H),4.20(4H),6.70 (1H),6.90(1H),7.13(1H), 7.53(1H),8.40(1H), 8.50(1H) |
| 94 | 1 | $-NMe_2$ |  |  | $C_{20}H_{17}N_3S$ oil | 3.13(3H),7.06(1H),7.30-7.80(6H),8.03(1H),8.38 (1H),8.53(1H) |

| Cmpd No. | No. of W. Ex. based | $R^1$ | $R^2$ | $R^3$ | Composition Formula m.p. |
|---|---|---|---|---|---|
| 95 | 1 | -NHEt |  |  | $C_{19}H_{19}N_3S$ 172-173° |
| 96 | 1 | -NHMe |  |  | $C_{19}H_{19}N_3S$ 158-159° |
| 97 | 1 | -NHEt |  |  | $C_{20}H_{21}N_3S$ 164-165° |
| 98 | 1 | -NHEt |  |  | $C_{17}H_{15}N_3O_2S$ 153-154° |
| 99 | 1 | -NHMe |  |  | $C_{17}H_{15}N_3O_2S$ 181-182° |
| 100 | 1 | -NHEt |  |  | $C_{18}H_{17}N_3O_2S$ 140-141° |
| 101 | 1 | -NHMe |  |  | $C_{19}H_{15}N_3S$ 183-184° |

Example 15

Examples of Pharmaceutical Composition

| A) Capsule | |
|---|---|
| (1) Compound No. 1 | 50 mg |
| (2) Cellulose fine powder | 45 mg |
| (3) Lactose | 52 mg |
| (4) Magnesium stearate | 13 mg |
| | Total 160 mg |

All the materials were mixed and filled into a gelatin capsule.

| B) Soft Capsule | |
|---|---|
| (1) Compound No. 7 | 20 mg |
| (2) Corn starch oil | 130 mg |
| | Total 150 mg |

A mixed solution of (1) and (2) were prepared and filled into a soft capsule by a conventional manner.

| C) Tablet | |
|---|---|
| (1) Compound No. 48 | 50 mg |
| (2) Lactose | 34 mg |
| (3) Corn starch | 10.6 mg |
| (4) Corn starch (gelatinized) | 5 mg |
| (5) Magnesium stearate | 0.4 mg |
| (6) Calcium Carboxymethyl cellulose | 20 mg |
| | Total 120 mg |

All the materials were mixed and compressed by a tabletting machine to prepare a tablet in accordance with a conventional manner.

Reference Example 1

In 300 mℓ of anhydrous tetrahydrofuran was dissolved 33.2 mℓ of diisopropylamine, and the solution was cooled to -78°C, to which was added dropwise, while stirring, 148 mℓ of hexane solution of n-butyl lithium (1.6 M). The mixture was stirred for further 10 minutes at the same temperature, followed by dropwise addition of 20 g of β-picoline. The temperature was then raised up to -10°-0°C and the mixture was stirred for 20 minutes, to which was added dropwise 19.4 g of ethyl p-anisole dissolved in 40 mℓ of anhydrous tetrahydrofuran. Then, the mixture was stirred for one hour at room temperature, followed by addition of about 100 mℓ of water. The organic solvent was evaporated off, and the concentrated solution was subjected to extraction with ethyl acetate. The extract solution was washed with water and dried on magnesium sulfate, followed by crystalliation from a mixture of ethyl acetate-isopropylether to give 20.8 g (yield: 85%) of 1-(4-methoxypheny1)-2-(3-pyridyl)-ethanone, m.p. 71-72°C.

By employing, instead of ethyl p-anisole, ethyl benzoate, ethyl 3,4-dimethoxybenzoate, ethyl 3,4,5-trimethoxybenzoate, ethyl 4-methoxymethoxy benzoate, methyl 4-fluorobenzoate, methyl 5-indanylcarboxylate, methyl 5,6,7,8-tetrahydro-2-naphthylcarboxylate,methyl 1,4-benzodioxan-6-carboxylate or methyl 2-naphthylcarboxylate, the process of the above Reference Example was conducted to give the following compounds, correspondingly:

1-phenyl-2-(3-pyridyl)ethanone, m.p. 44.5-45.5°C
1-(3,4-dimethoxyphenyl)-2-(3-pyridyl)ethanone m.p. 114-115°C
1-(3,4,5-trimethoxyphenyl)-2-(3-pyridyl)ethanone m.p. 104-105°C
1-(4-methoxymethoxyphenyl)-2-(3-pyridyl)ethanone m.p. 43-44°C
1-(4-fluorophenyl)-2-(3-pyridyl)ethanone, oily substance
1-(5-indanyl)-2-(3-pyridyl)ethanone m.p. 55-56°C
1-(5,6,7,8-tetrahydro-2-naphthyl)-2-(3-pyridyl)ethanone
m.p. 65-66°C

1-(1,4-benzodioxan-6-yl)-2-(3-pyridyl)ethanol m.p. 89-90 °C
1-(2-naphthyl)-2-(3-pyridyl)ethanone m.p. 69-70 °C
Likewise, instead of β-picoline, use of α-picoline,γ-picoline or 3.5-lutidine gives the following compounds, correspondingly:
1-phenyl-2-(2-pyridyl)ethanone, m.p. 59-60 °C
1-(4-methoxyphenyl)-2-(2-pyridyl)ethanone, m.p. 77-78 °C
1-phenyl-2-(4-pyridyl)ethanone, m.p. 109-110 °C
1-(4-methoxyphenyl)-2-(4-pyridyl)ethanone, m.p. 103-104 °C
1-phenyl-2-(5-methyl-3-pyridyl)ethanone, m.p. 53-54 °C
1-(4-ethylphenyl)-2-(3-pyridyl)ethanone, m.p. 80-81 °C
1-(3,4-methylenedioxyphenyl)-2-(3-pyridyl)ethanone, m.p. 98-99 °C

Reference Example 2

In 36 mℓ of acetic acid was dissolved 6.85g of 1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone obtained by Reference Example 1. To the solution was added 1.7 mℓ of bromine, and the mixture was stirred at 80 °C for 3 hours. The reaction solution was cooled with ice-water, and the resulting crystals were collected by filtration. The crystals were washed with ethanol and ethylether, successively, followed by drying to give 10.4g (yield 89%) of hydrobromide of 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone, m.p. 188-195 °C.
By a similar method to Reference Example 2, hydrobromides of the following compounds were obtained.
2-bromo-1-phenyl-2-(3-pyridyl)ethanone, m.p.*1 208-215 °C
2-bromo-1-(3,4-dimethoxyphenyl)-2-(3-pyridyl)ethanone, m.p.*1 191-193 °C
2-bromo-1-(3,4,5-trimethoxyphenyl)-2-(3-pyridyl)ethanone, m.p.*1 184-186 °C
2-bromo-1-(4-hydroxyphenyl)-2-(3-pyridyl)ethanone*2
2-bromo-1-(4-fluorophenyl)-2-(3-pyridyl)ethanone, m.p.*1 189-191 °C
2-bromo-1-phenyl-2-(2-pyridyl)ethanone, m.p.*1 180-181 °C
2-bromo-1-(4-methoxyphenyl)-2-(2-pyridyl)ethanone, m.p.*1 170-171 °C
2-bromo-1-phenyl-2-(4-pyridyl)ethane, m.p.*1 230-232 °C
2-bromo-1-(4-methoxyphenyl)-2-(4-pyridyl)ethanone, m.p.*1 207-209 °C
2-bromo-1-pheny-2-(5-methyl-3-pyridyl)ethanone, m.p.*1 189-193 °C
2-bromo-1-(4-ethylphenyl)-2-(3-pyridyl)ethanone, m.p.*1 145-146 °C
2-bromo-1-(3,4-methylenedioxyphenyl)-2-(3-pyridyl)ethanone, m.p.*1 174-175 °C
2-bromo-1-(5-indanyl)-2-(3-pyridyl)ethanone m.p. *1 177-178 °C
2-bromo-1-(5,6,7,8-tetrahydro-2-naphthyl)-2-(3-pyridyl)ethanone m.p. *1 160-162 °C
2-bromo-1-(1,4-benzodioxane-6-yl)-2-(3-pyridyl)ethanone *2
2-bromo-1-(2-naphthyl)-2-(3-pyridyl)ethanone m.p. *1 197-199 °C
The melting point bearing *1 is that of hydrobromide. The hydrobromide bearing *2 was directly used for thiazole-forming reaction without purification.

Reference Example 3

In 80mℓ of anhydrous tetrahydrofuran was dissolved 8.86mℓ of diisopropylamine. The solution was cooled to -10 °, to which was added dropwise 39.5mℓ of a hexanoic solution of n-butyl lithium (1.6M). Then, the mixture was stirred for 30 minutes at the same temperature, followed by dropwise addition of 5.34g of β-picoline. The mixture was stirred for 30 minutes, to which was added dropwise 5g of 5-methoxycarbonyl indane dissolved in 10mℓ of anhydrous tetrohydrofuran. Then, the mixture was stirred for one hour at room temperature, followed by addition of about 25mℓ of water. The organic solvent was exaporated off under reduced pressure. The concentrated solution was subjected to extraction with ethylacetate. The extract solution was washed with water, dried on magnesium sulfate and concentrated. The concentrate was crystallized from ethylacetate-isopropylether to give 5.6g(yield 82%) of 1-(5-indanyl)-2-(3-pyridyl)-ethanone, m.p. 55-56 °C.

Reference Example 4

In 20mℓ of acetic acid was dissolved 4.3g of 1-(5-indanyl)-2-(3-pyridyl)ethanone. To the solution was added 0.93mℓ of bromine, which was stirred for one hour at 80 °, then the reaction solution was cooled. Addition of 80mℓ of ethylether gives a layer of oily substance. The supernatant was discorded, and the remainder was dissolved in 50mℓ of acetonitrile. The solution was cooled to give 6.2g of 2-bromo-1-(5-

indanyl)-2-(3-pyridyl)ethanone hydrobromide, m.p. 176-177°C. The yield was 86%.

Reference Example 5

In 6mℓ of thionyl chloride was suspended 5.0g of piperonylic acid. The suspension was refluxed for 8 hours. Excess volume of thionyl chloride was evaporated off under reduced pressure to give crude crystals of piperonylic acid chloride.
The crystals were dissolved in 10mℓ of methylene chloride. The solution was slowly added dropwise, while stirring at 0°, to a solution of 1.7g of propylene imine and 3.3g of petroreum ether in 10mℓ of methylene chloride. Then, the mixture was further stirred for 30 minutes. The solvent was evaporated off under reduced pressure. To the residue was added water, which was subjected to extraction with ethyl acetate. The extract solution was washed with water, dried and concentrated under reduced pressure. Thus-obtained crude product was purified by means of a silica-gel chromatography (eluent: ethyl acetate) to give 4.37g (yield 69%) of N-piperonyloyl propylene imine.

Reference Example 6

A lithium diisopropyl amide solution was prepared at 0° from 3.2mℓ of diisopropylamine, 14.5mℓ of n-butyl lithium hexane solution (1.6M) and 60mℓ of tetrahydrofuran. To thus-prepared solution was added 1.95g of β-picoline, 2nd the mixture was stirred for 30 minutes at 0°. To the mixture was added slowly dropwise a tetrahydrofuran solution of 4.3g of N-piperonyl propylene imine, then the whole mixture was stirred for one hour. To the reaction solution was added N-hydrochloric acid until pH of the solution becomes acid side. The organic solvent was evaporated off under reduced pressure. The aqueous layer was made weakly alkaline by the use of an aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The extract solution was washed with water, dried and concentrated under reduced pressure. The residue was purified by means of a silica-gel column chromatography (eluent: ethyl acetate), followed by recrystallization from ethyl acetate-isopropyl ether to give 3.2g (yield : 63%) of 1-piperonyl-2-(3-pyridyl)ethanone, m.p. 98-99°C.

Experimental Example

A. Anti-inflammatory activity; Carrageenin edema (C.E. Method)

The anti-inflammatory activities of test compounds were estimated in a group [Six Jcl: SD rats (male, weighing 180-220 g)] by the method of Winter et al. [Proc. Soc. Exp. Biol. Med, 111, 544 (1962)].
After measuring the volume of the right-hind paw(a), the rats were given orally 5 mℓ of water. One hour after oral administration of the test compounds, 0.05 mℓ each of a 1% carrageenin solution in physiological saline was subcutaneously injected at the sole of right-hind paw. Three hr. later, the volume of the right-hind paw was measured(b). The volume of edema was obtained from the difference (a-b) between the two volumes. By comparing the volume of edema of the group, to which test compound was administered, with that of the group, to which no test compound was administered, an inhibitory effect of the compound on the edema was determined.

B. Analgesic action: Phenylquinone writhing syndrome (P.Q. Method)

The test was conducted by following the method Siegmund et al. [Proc. Soc. exp. Biol. Med. 95, 729 (1957).] employing a group [ten Slc:ICR mice (male, 4-weeks old, weighing 20±2g)]. Test compounds were administered orally 30 minutes before intraperitoneal injection of 0.02% phenylquinone by 0.1 mℓ/body weight of 10 g. Then, the frequency of responses, i.e. writhing and stretching was counted in each animal for 20 minutes. The average frequencies in the test group and the control group were compared, and an inhibitory effect of the compounds on this response was determined.

C. Water-immersion stress-induced gastric ulcer (W.I. Method)

Male SD rats (7-weeks old, weighing 190-240 g) were used after a 24 hr. fast in groups of six animals. According to the method of Takagi and Okabe [Jpn. J. Pharmacol., 18, 9 (1968)], the animals were placed in a stress cage made of stainless steel and immersed vertically to the level of xiphoid process in a water bath maintained at 23°C for five hours. The length (mm) of individual lesions in fundic mucosa was

measured under a dissecting microscope with a 1-mm square-grid eye piece (X 10), and the sum of the length of individual lesions for each stomach was used as an ulcer index. The ulcer index of the test group was compared with that of the control group, and the inhibition ratio was calculated.

D. Acute toxicity Test in mice

Five-weeks old ICR-male mice were used in groups of five animals. Each animal was orally administered with 500 mg/kg of each test compound. Then, during the subsequent one week, the number of dead animals was counted. Representable examples of the results of the foregoing tests were shown in Table 2.

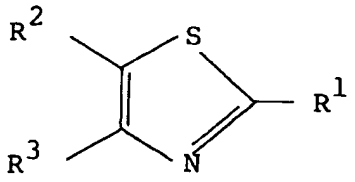
Table 2

| Cmpd No | C.E. Method | P.Q. Method 50mg/kg | W.I. Method 50mg/kg | Acute Toxicity |
|---|---|---|---|---|
| 1 | 60 | 96.8 | 86 | 0/5 |
| 2 | 77.1 | 52.6 (25mg/kg) | 70 | 0/5 |
| 4 | 63.7 | 78.9 | 74 | 0/5 |
| 9 | 16.9 | 40.5 | 71 | 0/5 |
| 13 | 7.0 | 67.5 | 66 | 0/5 |
| 17 | 48.2 | 80.7 | 79 | 0/5 |
| 28 | 15.7 | 63.3 | 33 | 0/5 |

**Claims**

**Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. A compound of the formula:



(I)

wherein

$R_1$ is (1) a $C_{1-10}$alkyl group unsubstituted or substituted by $C_{1-4}$alkylamino or carboxyl, (2) a phenyl group unsubstituted or substituted by carboxyl, (3) a $C_{3-7}$cycloalkyl group, (4) an amino group unsubstituted or substituted by $C_{1-4}$alkyl, phenyl or pyridyl, (5) a piperidino group or (6) a morpholino group,

$R_2$ is a pyridyl group unsubstituted or substituted by $C_{1-4}$alkyl, and

$R_3$ is a naphthyl or a phenyl group unsubstituted or substituted by $C_{1-4}$alkoxy, hydroxy, halogen, methylenedioxy or trimethylene,

or a salt thereof.

2. A compound as claimed in claim 1, wherein the salt is a pharmacologically acceptable salt.

3. A compound as claimed in claim 1, wherein $R^2$ is 3-pyridyl group which may be substituted with methyl.

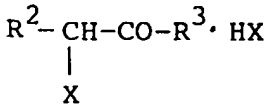
4. A compound as claimed in claim 1, wherein the compound is 4-(4-methoxyphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazole.

5. A compound as claimed in claim 1, wherein the compound is 4-(4-fluorophenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazole.

6. A compound as claimed in claim 1, wherein the compound is 4-(3,4-methylenedioxyphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazole.

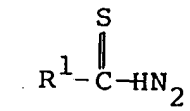
7. An analgesic, anti-pyretic, anti-inflammatory and anti-ulcer pharmaceutical composition, which comprises, as an active ingredient, an effective amount of a compound as claimed in claim 1, or a salt thereof, and a pharmaceutically acceptable carrier therefor.

8. A method of preparing a 1,3-thiazole derivative as claimed in claim 1, or a salt thereof, characterised by allowing a compound representable by the general formula;



(II)

[wherein $R^2$ and $R^3$ have the meanings defined in claim 1, and X stands for a halogen atom]
to react with a compound representable by the general formula;

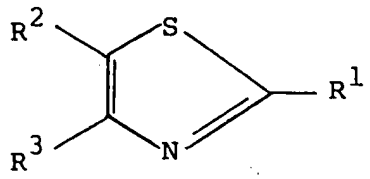


(III)

[wherein $R^1$ has the meaning defined in claim 1.

**Claims for the following Contracting State : AT**

1. A method of preparing 1,3-thiazole derivatives representable by the general formula:



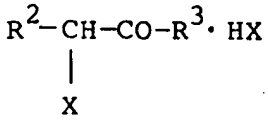
wherein

$R_1$ is (1) a $C_{1-10}$alkyl group unsubstituted or substituted by $C_{1-4}$alkylamino or carboxyl, (2) a phenyl group unsubstituted or substituted by carboxyl, (3) a $C_{3-7}$cycloalkyl group, (4) an amino group unsubstituted or substituted by $C_{1-4}$alkyl, phenyl or pyridyl, (5) a piperidino group or (6) a morpholino group,

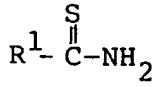
$R_2$ is a pyridyl group unsubstituted or substituted by $C_{1-4}$alkyl, and

$R_3$ is a naphthyl or a phenyl group unsubstituted or substituted by $C_{1-4}$alkoxy, hydroxy, halogen, methylenedioxy or trimethylene,

or a salt thereof, characterised by allowing a compound representable by the general formula;



[wherein $R^2$ and $R^3$ have the meanings given above, and X stands for a halogen atom] to react with a compound representable by the general formula;



[wherein $R^1$ has the meaning given above].

2. A method as claimed in claim 1, wherein the salt is a pharmacologically acceptable salt.

3. A method as claimed in claim 1, wherein $R^2$ is 3-pyridyl group which may be substituted with methyl.

4. A method as claimed in claim 1, wherein the compound is 4-(4-methoxyphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazole.

5. A method as claimed in claim 1, wherein the compound is 4-(4-fluorophenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazole.

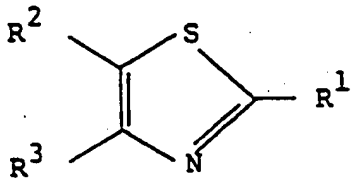
6. A method as claimed in claim 1, wherein the compound is 4-(3,4-methylenedioxyphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazole.

7. An analgesic, anti-pyretic, anti-inflammatory and anti-ulcer pharmaceutical composition, which comprises, as an active ingredient, an effective amount of a compound as claimed in claim 1, or a salt thereof, and a pharmaceutically acceptable carrier therefor.

**Patentansprüche**

**Patentanspruch für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. Verbindung der Formel:



(I)

worin

$R^1$ (1) eine unsubstituierte oder durch $C_{1-4}$-Alkylamino oder Carboxyl substituierte $C_{1-10}$-Alkylgruppe, (2) eine unsubstituierte oder durch Carboxyl substituierte Phenylgruppe, (3) eine $C_{3-7}$-Cykloalkylgruppe, (4) eine unsubstituierte oder durch $C_{1-4}$-Alkyl, Phenyl oder Pyridyl substituierte Aminogruppe, (5) eine Piperidinogruppe oder (6) eine Morpholinogruppe ist,

$R^2$ eine unsubstituierte oder durch $C_{1-4}$-Alkyl substituierte Pyridylgruppe ist und

$R^3$ eine unsubstituierte oder durch $C_{1-4}$-Alkoxy, Hydroxy, Halogen, Methylendioxy oder Trimethylen substituierte Naphthyl- oder Phenylgruppe ist,

oder ein Salz davon.

2. Verbindung nach Anspruch 1, worin das Salz ein pharmakologisch verträgliches Salz ist.

3. Verbindung nach Anspruch 1, worin $R^2$ eine 3-Pyridylgruppe ist, die mit Methyl substituiert sein kann.

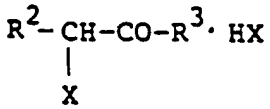
4. Verbindung nach Anspruch 1, worin die Verbindung 4-(4-Methoxyphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazol ist.

5. Verbindung nach Anspruch 1, worin die Verbindung 4-(4-Fluorphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazol ist.

6. Verbindung nach Anspruch 1, worin die Verbindung 4-(3,4-Methylendioxyphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazol ist.

7. Analgetische, antipyretische, antiinflammatorische und antiulkuswirksame pharmazeutische Zusammensetzung, die als einen Wirkstoff eine wirksame Menge einer Verbindung nach Anspruch 1 oder eines Salzes davon und einen pharmazeutisch verträglichen Träger dafür umfaßt.

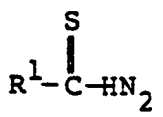
8. Verfahren zur Herstellung eines 1,3-Thiazolderivats nach Anspruch 1 oder eines Salzes davon, gekennzeichnet durch das Umsetzenlassen einer Verbindung der allgemeinen Formel:



(II)

[worin $R^2$ und $R^3$ die in Anspruch 1 definierten Bedeutungen haben und X für ein Halogenatom steht]

mit einer Verbindung der allgemeinen Formel:

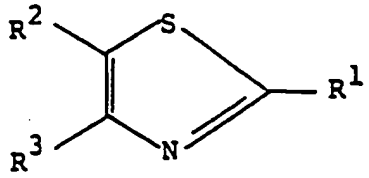


(III)

[worin $R^1$ die in Anspruch 1 definierte Bedeutung hat].

**Patentansprüche für folgenden Vertragsstaat : AT**

1. Verfahren zur Herstellung von 1,3-Thiazolderivaten der allgemeinen Formel:



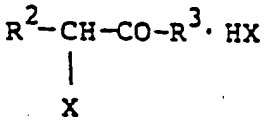
worin

$R^1$ (1) eine unsubstituierte oder durch $C_{1-4}$-Alkylamino oder Carboxyl substituierte $C_{1-10}$-Alkylgruppe, (2) eine unsubstituierte oder durch Carboxyl substituierte Phenylgruppe, (3) eine $C_{3-7}$-Cykloalkylgruppe,(4) eine unsubstituierte oder durch $C_{1-4}$-Alkyl, Phenyl oder Pyridyl substituierte Aminogruppe, (5) eine Piperidinogruppe oder (6) eine Morpholinogruppe ist,

$R^2$ eine unsubstituierte oder durch $C_{1-4}$-Alkyl substituierte Pyridylgruppe ist und

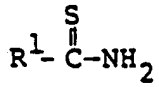
$R^3$ eine unsubstituierte oder durch $C_{1-4}$-Alkoxy, Hydroxy, Halogen, Methylendioxy oder Trimethylen substituierte Naphthyl- oder Phenylgruppe ist,

oder ein Salz davon, gekennzeichnet durch das Umsetzenlassen einer Verbindung der allgemeinen Formel:



[worin $R^2$ und $R^3$ die oben angeführten Bedeutungen haben und X für ein Halogenatom steht]

mit einer Verbindung der allgemeinen Formel:



[worin $R^1$ die oben angeführte Bedeutung hat].

2. Verfahren nach Anspruch 1, worin das Salz ein pharmakologisch verträgliches Salz ist.

3. Verfahren nach Anspruch 1, worin $R^2$ eine 3-Pyridylgruppe ist, die mit Methyl substituiert sein kann.

4. Verfahren nach Anspruch 1, worin die Verbindung 4-(4-Methoxyphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazol ist.

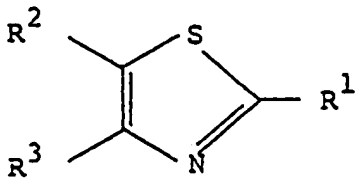
5. Verfahren nach Anspruch 1, worin die Verbindung 4-(4-Fluorphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazol ist.

6. Verfahren nach Anspruch 1, worin die Verbindung 4-(3,4-Methylendioxyphenyl)-2-methylamino-5-(3-pyridyl)-1,3-thiazol ist.

7. Analgetische, antipyretische, antiinflammatorische und antiulkuswirksame pharmazeutische Zusammensetzung, die als einen Wirkstoff eine wirksame Menge einer Verbindung nach Anspruch 1 oder eines Salzes davon und einen pharmazeutisch verträglichen Träger dafür umfaßt.

**R v ndications**
**Revendications pour l s Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. Composé de formule:



(I)

dans laquelle $R_1$ est (1) un groupe alcoyle en $C_{1-10}$ non substitué ou substitué par un alcoylamino en $C_{1-4}$ ou par un carboxyle, (2) un groupe phényle non substitué ou substitué par un carboxyle, (3) un groupe cycloalcoyle en $C_{3-7}$, (4) un groupe aminé non substitué ou substitué par un alcoyle en $C_{1-4}$, un phényle ou un pyridyle, (5) un groupe pipéridino ou (6) un groupe morpholino,

$R_2$ est un groupe pyridyle non substitué ou substitué par un alcoyle en $C_{1-4}$ et

$R_3$ est un groupe naphtyle ou phényle non substitué ou substitué par un alcoxy en $C_{1-4}$, un hydroxy, un halogène, un méthylènedioxy ou un triméthylène,

ou un sel de ce composé.

2. Composé selon la revendication 1, dans lequel le sel est un sel pharmacologiquement acceptable.

3. Composé selon la revendication 1, dans lequel $R^2$ est un groupe 3-pyridyle qui peut être substitué par un méthyle.

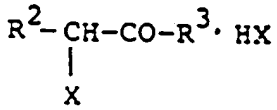
4. Composé selon la revendication 1, qui est le 4-(4-méthoxyphényl)-2-méthylamino-5-(3-pyridyl)-1,3-thiazole.

5. Composé selon la revendication 1, qui est le 4-(4-fluorophényl)-2-méthylamino-5-(3-pyridyl)-1,3-thiazole.

6. Composé selon la revendication 1, qui est le 4-(3,4-méthylènedioxyphényl)-2-méthylamino-5-(3-pyridyl)-1,3-thiazole.

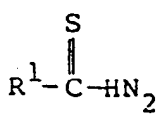
7. Composition pharmaceutique analgésique, antipyrétique, anti-inflammatoire et antiulcérative, qui comprend comme substance active une quantité efficace d'un composé selon la revendication 1 ou d'un sel de celui-ci et un véhicule pharmaceutiquement acceptable.

8. Procédé de préparation d'un dérivé de 1,3-thiazole selon la revendication 1 ou d'un sel de celui-ci, caractérisé en ce que l'on fait réagir un composé répondant à la formule générale:



(II)

dans laquelle $R^2$ et $R^3$ ont les significations indiquées à la revendication 1 et X représente un atome d'halogène, avec un composé répondant à la formule générale:

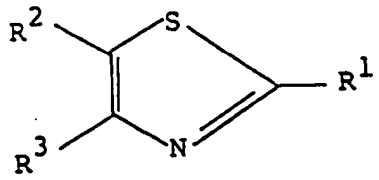


(III)

dans laquelle $R^1$ a la signification indiquée à la revendication 1.

**Revendications pour l'Etat contractant suivant : AT**

1. Procédé de préparation de dérivés de 1,3-thiazole répondant à la formule générale

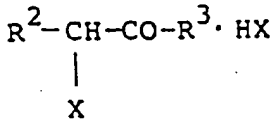


dans laquelle $R_1$ est (1) un groupe alcoyle en $C_{1-10}$ non substitué ou substitué par un alcoylamino en $C_{1-4}$ ou par un carboxyle, (2) un groupe phényle non substitué ou substitué par un carboxyle, (3) un groupe cycloalcoyle en $C_{3-7}$, (4) un groupe aminé non substitué ou substitué par un alcoyle en $C_{1-4}$, un phényle ou un pyridyle, (5) un groupe pipéridino ou (6) un groupe morpholino,

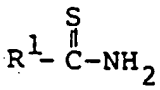
$R_2$ est un groupe pyridyle non substitué ou substitué par un alcoyle en $C_{1-4}$ et

$R_3$ est un groupe naphtyle ou phényle non substitué ou substitué par un alcoxy en $C_{1-4}$, un hydroxy, un halogène, un méthylènedioxy ou un triméthylène,

ou d'un sel de ces composés, caractérisé en ce que l'on fait réagir un composé répondant à la formule générale:



dans laquelle $R^2$ et $R^3$ ont les significations indiquées à la revendication 1 et X représente un atome d'halogène, avec un composé répondant à la formule générale:



dans laquelle $R^1$ a la signification indiquée à la revendication 1.

2. Procédé selon la revendication 1, dans lequel le sel est un sel pharmacologiquement acceptable.

3. Procédé selon la revendication 1, dans lequel $R^2$ est un groupe 3-pyridyle qui peut être substitué par un méthyle.

4. Procédé selon la revendication 1, dans lequel le composé est le 4-(4-méthoxyphényl)-2-méthylamino-5-(3-pyridyl)-1,3-thiazole.

5. Procédé selon la revendication 1, dans lequel le composé est le 4-(4-fluorophényl)-2-méthylamino-5-(3-pyridyl)-1,3-thiazole.

6. Procédé selon la revendication 1, dans lequel le composé 4-(3,4-méthylènedioxyphényl)-2-méthylamino-5-(3-pyridyl)-1,3-thiazole.

7. Composition pharmaceutique analgésique, antipyrétique, anti-inflammatoire et antiulcérative, qui comprend comme substance active une quantité efficace d'un composé selon la revendication 1 ou d'un sel de celui-ci et un véhicule pharmaceutiquement acceptable.